Dynamic chromatin states in human ES cells reveal potential regulatory sequences and genes involved in pluripotency.

Journal: Cell Res

Publication Year: 2011

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PubMed link: 21876557

Funding Grants: Mapping the transcriptional regulatory elements in the genome of hESC, Mechanisms of chromatin dynamics at enhancers during ES cell differentiation

Public Summary:
Human embryonic stem (ES) cells have the unique ability to differentiate into nearly any cell type in the human body. During the process of differentiation, ES cells undergo changes in epigenetic structure, such as DNA methylation and post-translational modifications of histones, to bring about changes in gene expression that confer the differentiated state. However, little is known about how the epigenome changes during differentiation. To address this defiency, we have examined the dynamics of chromatin modifications in human ES cells undergoing differentiation into a mesendodermal lineage. We find that while the epigenetic state of promoters remains largely invariant upon differentiation, histone modifications found at enhancers change dramatically. Fascinatingly, a pre-existing epigenetic signature at enhancers in ES cells is indicative of a poised state that may affect differentiation potential. Our results provide new evidence supporting the role of the epigenome in defining enhancers and differentiation.

Scientific Abstract:
Pluripotency, the ability of a cell to differentiate and give rise to all embryonic lineages, defines a small number of mammalian cell types such as embryonic stem (ES) cells. While it has been generally held that pluripotency is the product of a transcriptional regulatory network that activates and maintains the expression of key stem cell genes, accumulating evidence is pointing to a critical role for epigenetic processes in establishing and safeguarding the pluripotency of ES cells, as well as maintaining the identity of differentiated cell types. In order to better understand the role of epigenetic mechanisms in pluripotency, we have examined the dynamics of chromatin modifications genome-wide in human ES cells (hESCs) undergoing differentiation into a mesendodermal lineage. We found that chromatin modifications at promoters remain largely invariant during differentiation, except at a small number of promoters where a dynamic switch between acetylation and methylation at H3K27 marks the transition between activation and silencing of gene expression, suggesting a hierarchy in cell fate commitment over most differentially expressed genes. We also mapped over 50 000 potential enhancers, and observed much greater dynamics in chromatin modifications, especially H3K4me1 and H3K27ac, which correlate with expression of their potential target genes. Further analysis of these enhancers revealed potentially key transcriptional regulators of pluripotency and a chromatin signature indicative of a poised state that may confer developmental competence in hESCs. Our results provide new evidence supporting the role of chromatin modifications in defining enhancers and pluripotency.